



TITLE:

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CITATION:

Kita, Masafumi ...[et al]. Adrenalectomy for metastatic adrenal tumors. 泌尿器科紀要 2007, 53(11): 761-766

ISSUE DATE:

2007-11

URL:

<http://hdl.handle.net/2433/71529>

RIGHT:

ADRENALECTOMY FOR METASTATIC ADRENAL TUMORS

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The indications for adrenalectomy in cases of metastatic adrenal tumor remain controversial. To clarify indications and outcomes of adrenalectomy for adrenal metastasis, we performed a retrospective review of all 8 patients who underwent adrenalectomy for adrenal metastasis between 1990 and 2006 in Asahikawa Medical College Hospital. The Primary tumor was renal cell carcinoma in 2 cases, and eccrine poro carcinoma, rectal cancer, lung cancer, melanoma, bladder cancer and cancer of unknown origin in 1 case each. Open adrenalectomy was performed in all cases, including 1 case that was converted from laparoscopic adrenalectomy. Of the 4 patients with solitary adrenal metastasis, 3 were considered tumor-free after adrenalectomy, while the remaining patient was not due to unresectable primary tumor. Of the 3 patients with complete resection, one remained alive as of 88 months after adrenalectomy but was then lost to follow-up, and the other 2 patients remain alive 12 and 7 months after adrenalectomy. Of the 2 patients with other resectable metastasis who were tumor-free after removal of all metastases, one was alive 31 months postoperatively and the other died 23 months after operation. The remaining 2 cases with other unresectable metastasis died within 6 months after adrenalectomy. At least in cases of solitary adrenal metastasis, adrenalectomy can be effective if other valid methods are unavailable.

(Hinyokika Kiyo **53** : 761–766, 2007)

Key words : Adrenal metastasis, Adrenalectomy, Treatment outcome

INTRODUCTION

Metastasis to the adrenal gland is frequently found at autopsy and, per unit weight, the adrenal gland is the organ to which other malignant tumors metastasize most frequently^{1,2)}. Adrenal metastasis from non-adrenal cancer has been considered a sign of disease dissemination, and unsuitable for surgical removal. Recently, however, continuing progress in imaging modalities has enabled the detection of adrenal metastasis in the early stages at the time of presentation or follow-up for non-adrenal malignancies. With the increasing number of such cases, surgical removal of adrenal metastasis has been reported^{3–6)}. Although several reports have shown the advantage of adrenalectomy, a randomized prospective study to examine whether surgical removal of adrenal metastasis offers beneficial outcomes and prolongs patient survival would be difficult to implement. The indications for adrenalectomy thus remain controversial. To clarify indications and outcomes associated with adrenalectomy for adrenal metastasis, we reviewed cases of adrenal metastasis surgically removed in our institution. We also examined the relevant literature and discuss herein the diagnosis of metastatic adrenal tumor and indications of adrenalectomy for metastatic adrenal tumor.

METHODS

A retrospective review of 99 patients who underwent adrenalectomy between 1990 and 2006 in Asahikawa

Medical College Hospital revealed 8 cases of adrenal metastases. In all cases, computed tomography (CT), magnetic resonance imaging (MRI) and/or various scintigraphies were performed for evaluation of adrenal metastasis and other metastases. Fundamentally, the aim of adrenalectomy is to leave the patient tumor-free after operation by resecting all gross metastasis. However, adrenalectomy was performed with curative intent in restricted cases with unresectable but well-controlled metastasis following other treatment. Synchronous metastasis was defined as metastasis recognized at the time of primary tumor diagnosis. Cases with adrenal metastasis or direct extension from ipsilateral synchronous renal cell carcinoma were excluded from this study. Follow-up period was measured as the time from adrenalectomy until death or last known contact. In all cases, imaging findings, serum and urine hormonal levels and other medical data were reviewed. Pathological diagnosis was made by a single pathologist.

RESULTS

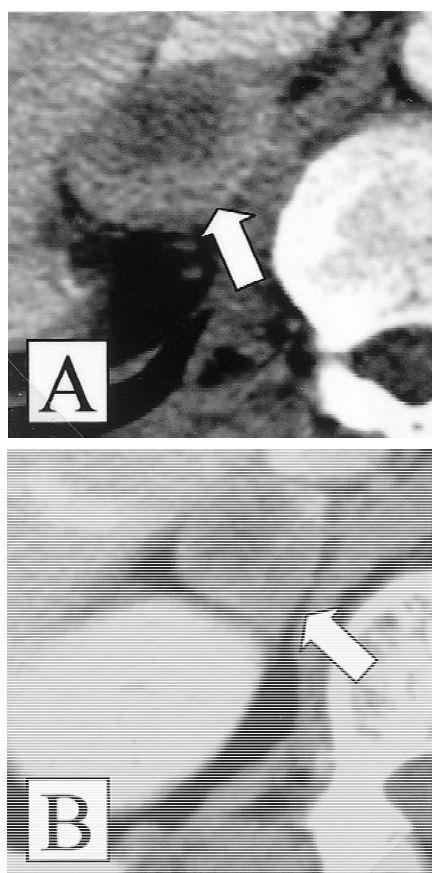
Mean age of the 8 patients (7 men, 1 woman) who underwent adrenalectomy for metastatic adrenal tumor was 57.7 years and mean tumor size was 36.8 mm (Table 1). No patient showed any symptoms due to adrenocortical or adrenomedullary hormonal disturbance.

In all cases, preoperative diagnosis was made using CT, MRI and/or adrenal scintigraphy. Fig. 1 shows representative findings from contrast-enhanced CT of a typical case, with peripheral enhancement and hetero-

Table 1. Characteristics and clinical course of each patient who underwent adrenalectomy for metastatic adrenal tumor

No.	Age	Gender	Tumor size (mm)	Primary tumor	Management of primary tumor	Other metastasis (management)	Syn. or Met.	DFI (months)	Status	Survival (months)
1	61	Male	30	Ecrrine gland	Surgery	No	Met.	46	Lost to follow-up	88
2	45	Male	45	Rectum	Surgery, Chemotherapy	No	Syn.	—	Alive	12
3	53	Female	35	Melanoma	Surgery	No	Met.	5	Alive	7
4	52	Male	40	Lung	Chemotherapy	No	Syn.	—	Died	11
5	72	Male	45	Kidney	Surgery	Opposite kidney (surgery)	Met.	48	Lost to follow-up	31
6	64	Male	22	Unknown	Chemotherapy	Bone (surgery)	Syn.	—	Died	23
7	58	Male	32	Bladder	Surgery, Chemotherapy	Bone (radiotherapy)	Syn.	—	Died	2
8	57	Male	46	Kidney	Surgery	Bone (radiotherapy)	Met.	49	Died	6

LA = laparoscopic adrenalectomy; Syn = synchronous; Met = metachronous; DFI = disease-free interval (until appearance of adrenal metastasis in metachronous case).

**Fig. 1.** Contrast-enhanced CT findings of typical cases (A: case 2, B: case 7).

geneous contrast inside the tumor. No signs of local invasion such as irregular tumor margins or thickened frond-like structures around the periadrenal space were seen in any cases.

Primary tumor was renal cell carcinoma in 2 cases, and ecrrine poro carcinoma, rectal cancer, lung cancer, melanoma, bladder cancer and cancer of unknown origin in 1 case each (Table 1). Open adrenalectomy was performed in all cases, including 1 case converted from laparoscopic adrenalectomy. In another case, complete

resection was impossible due to severe adhesion of the adrenal tumor to the liver and vena cava. Synchronous presentation of both primary tumor and adrenal metastasis was seen in 4 patients. In the 4 patients with metachronous adrenal metastasis, mean duration between presentation of primary tumor and detection of adrenal metastasis was 47.7 months (Table 1). Depending on adrenal metastasis only or association with other metastasis and resectability of other metastasis, the 8 cases were divided into the following 3 groups.

Solitary adrenal metastasis (Cases 1–4)

In these 4 cases, adrenal metastasis was isolated. Adrenal tumor was removed by open surgery with an abdominal approach in 2 cases and a thoracoabdominal approach in the other 2 cases. In Cases 1–3, primary tumor was surgically resectable. Accordingly, these cases were considered disease-free after removal of the solitary adrenal metastasis and good prognosis was expected. Case 1 remained alive 88 months after adrenalectomy, but was then lost to follow-up. Cases 2 and 3 are currently alive as of 12 and 7 months after adrenalectomy. In Case 4, although adrenal metastasis was solitary, the primary tumor (lung cancer) was unresectable, so chemotherapy was performed. This patient died from multiple metastases 11 months after adrenalectomy.

Adrenal metastasis with other resectable metastasis (Cases 5 and 6)

In these 2 cases, other metastases were present at the time of adrenalectomy and these other metastases were removed simultaneously at the time of adrenalectomy. These 2 cases were thus considered tumor-free after removal of all metastases. Case 5 was alive 31 months postoperatively, and the other patient died 23 months after operation.

Adrenal metastasis with other unresectable metastasis (Cases 7 and 8)

These 2 cases had unresectable bone metastasis that was treated by radiotherapy (with addition of chemo-

therapy in Case 7). In Case 7, the patient was young and chemotherapy alone was considered insufficient treatment. In Case 8, bone metastasis was well-controlled by radiotherapy and no progression was seen for the 2 years after radiotherapy. Adrenalectomy was thus performed as a part of multidisciplinary treatment for these patients. However, the patients died from primary cancer at 2 and 6 months after adrenalectomy.

DISCUSSION

When adrenal tumor is found in patients who had or have non-adrenal malignancies, 3 questions arise: what is the nature of adrenal tumor; what are the indications for adrenalectomy; and what methods of adrenalectomy are applicable? These 3 issues are discussed individually below.

The diagnosis of metastatic adrenal tumor is not always straightforward. Patients with metastatic adrenal tumor are typically asymptomatic. Hormonal disturbance was not clinically detected in any patients in the present study. Metastatic adrenal tumor often shows defect of uptake on adrenal scintigraphy. On CT, metastatic adrenal tumor is characterized as higher attenuation value compared with adrenal adenoma on non-enhanced CT and as gradual wash-out of contrast medium on delayed contrast-enhanced CT⁷⁾. On chemical shift MRI, metastatic adrenal tumor shows a lack of lipid intensity⁸⁾. Boland et al.⁹⁾ evaluated positron emission tomography for 24 adrenal masses in patients with internal malignancy, and reported 100% accuracy for the diagnosis of metastatic adrenal tumor. Adrenal core biopsy is another method of diagnosis. Saeger et al.¹⁰⁾ reported the first prospective multicenter study to evaluate the diagnostic accuracy of adrenal core biopsy. That series obtained 211 specimens and reported a sensitivity of 90.9% and specificity of 95.4% for adrenal metastasis. Conversely, complications related to adrenal core biopsy, such as hemorrhage, pneumothorax and needle track tumor seeding, were certainly well documented^{11,12)}. The indications for adrenal core biopsy should thus be considered carefully. Generally, solitary adrenal metastasis might be difficult to distinguish from benign adrenal tumor using imaging techniques alone. In such cases, adrenal biopsy can be useful for diagnosis.

The second issue is the indication of adrenalectomy for metastatic adrenal tumor. Patrick et al.¹³⁾ reported the first case of adrenalectomy for adrenal metastases from non-small cell lung cancer. Since then, several reports have described adrenalectomy for adrenal metastasis, particularly from non-small cell lung cancer¹⁴⁻¹⁶⁾. These authors emphasized the advantages of adrenalectomy for metastatic adrenal tumor from non-small cell lung cancer. On the other hand, the guidelines of the American Society of Clinical Oncology for the treatment of unresectable non-small-cell lung cancer do not recommend routine adrenalectomy for solitary adrenal metas-

tasis because of insufficient evidence¹⁷⁾. Certainly, the prognosis of patients with extirpated adrenal metastasis is largely influenced by the biological behavior and degree of spread of primary malignancy. In our series, 3 cases (Cases 1-3) displayed primary tumor that was well controlled, with complete resection of solitary adrenal metastasis, resulting in a good prognosis following the surgical procedure. Kim et al.⁴⁾ reported 37 cases with solitary adrenal metastasis treated using adrenalectomy. Median survival was 21 months, and 5 patients survived > 5 years. Paul et al.⁵⁾ reviewed 77 cases of solitary adrenal metastasis treated by adrenalectomy and reported a median survival of 23 months. Primary tumor site was identified as having a significant impact on post-adrenalectomy survival. They reported that patients with kidney, colon or lung cancer or melanoma as primary site showed relatively good prognosis. Based on our data and a review of the literature, the most appropriate indications for adrenalectomy of metastatic adrenal tumor are; 1) well-controlled primary cancer, 2) solitary adrenal metastasis, 3) long disease-free interval (> 6 months⁴⁾) in metachronous cases, and 4) kidney, colon or lung cancer or melanoma as the primary site⁵⁾.

The last issue is the method of adrenalectomy, as either open or laparoscopic surgery. Laparoscopic surgery for the adrenal gland was first reported in 1992¹⁸⁾. Since then, many investigators have compared this procedure with conventional open adrenalectomy. With technological advances, laparoscopic adrenalectomy has become the gold-standard approach for benign surgical adrenal disorders, offering decreased morbidity, shorter length of hospitalization, more rapid convalescence and improved cosmesis compared with open adrenalectomy¹⁹⁾. Conversely, for malignant adrenal tumor, the indications and feasibility of laparoscopic adrenalectomy have not yet been established. To clarify the problems concerning laparoscopic adrenalectomy for malignancy, we summarized previous articles in which details were available and a certain number of cases were involved (Table 2). The total number of adrenal tumors we collected was 127, including not only metastatic tumors, but also adrenal carcinoma. Mean tumor size was 5.2 cm at the major axis. The mean operating time was 164 min and mean blood loss was 264 ml. These parameters do not seem particularly excessive compared with laparoscopic adrenalectomy for benign tumor. However, in 7.8% of the cases, resection of adjacent organs was required due to local invasion, and the rate of conversion to open surgery was 5.3%. Mean follow-up was about 22 months and the local recurrence rate was 10.2%. Simple comparison of the recurrence rate of laparoscopic adrenalectomy with that of open adrenalectomy is unreasonable. Salera et al.²⁴⁾ examined 11 cases of laparoscopic adrenalectomy and 30 cases of open adrenalectomy. Rate of positive resection margins was

Table 2. Review of laparoscopic adrenalectomy for malignancy

Cases	121
Adrenal tumors	127
Primary site	
Lung	43
Kidney	24
Adrenal	21
Colon	11
Melanoma	5
Others	22
Tumor size* (cm)	5.2
Operating time* (min)	164
Blood loss* (ml)	264
Resection rate of adjacent organ (%)	7.8
Open conversion rate (%)	6.2
Local recurrence rate (%)	10.2
Follow-up* (month)	21.6

* Mean value.

similar in each group, and no significant difference in overall survival was identified. Moinzadeh et al.²⁷⁾ reported that laparoscopic radical adrenalectomy for malignancy could be performed with acceptable outcomes (local recurrence rate, 23%, with no port-site metastases). However, serious case reports have questioned the indication of laparoscopic adrenalectomy for malignant tumor given the occurrence of local recurrence, port-site recurrence and carcinomatosis shortly after laparoscopic adrenalectomy (within 4–14 months)²⁷⁾. In our series, we tried laparoscopic surgery for 1 patient but had to perform open surgery due to severe adhesion of the tumor to periadrenal tissue. Until the indications and feasibility of laparoscopic adrenalectomy for adrenal malignancy are established, laparoscopic surgery for adrenal malignancy should be used with caution.

CONCLUSIONS

Consensus on the treatment for metastatic adrenal tumor is still not established. However, based on our experiences, adrenalectomy for metastatic adrenal tumor seems to provide long-term survival in certain cases. At least in cases of solitary adrenal metastasis, adrenalectomy can be effective treatment if other valid therapeutic methods are unavailable.

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(Received on February 5, 2007)
 (Accepted on May 6, 2007)

和文抄録

外科的治療を施行した転移性副腎腫瘍の検討

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転移性副腎腫瘍に対する副腎摘除術の適応に関してはまだ統一された見解はない。そこでその適応と治療効果を明らかにするために、1990年から2006年までの間に当院において転移性副腎腫瘍に対し副腎摘除術を施行した8症例について retrospective に検討した。全例開腹にて副腎摘除を施行しており、1例は腹腔鏡下摘出術からの移行であった。孤立性副腎転移は4例に認められ、3例が術後 tumor free となり得た。これら

3例の観察期間はそれぞれ88, 12, 7カ月であった。副腎以外にも転移を認めたが、副腎も含めてすべて外科的切除が可能であった2例はそれぞれ31, 23カ月の観察期間であった。副腎以外に切除不能な転移を認めた2例は6カ月以内に死亡した。他に有効な治療がない場合、少なくとも孤立性副腎転移に関しては副腎摘除が有効な治療となる可能性があると思われた。

(泌尿紀要 53 : 761-766, 2007)